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Dural arachnoid granulations and “giant” arachnoid granulations

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Abstract Although arachnoid granulations (AGs) were already described by Antonio Pacchioni more than 300 years ago, two issues draw particular attention: first, the radiological features and differential diagnosis of the so-called giant AGs (GAGs) and second, their possible association with various disease processes. In order to evaluate the frequency, size and normal distribution of GAGs, an anatomical study of the dural sinuses was carried out. It involved all the autopsies performed during the period August 2002–February 2005 and included 651 cases: 306 females and 345 males, aged 13–99 years (mean 69 years). Grossly visible GAGs were identified in 24 cases: 7 females and 17 males, aged 45–92 years (mean 69 years). This is the largest population-based anatomical study on GAGs. It shows that GAGs, in general a rare finding (3.68%), are rather common in the adult population, especially in the elderly (aged >65 years) and that they can reach remarkable size (up to 2.5 cm and more in diameter). Giant AGs should be considered in the radiological differential diagnosis of intradural lesions, particularly those occurring in the transverse sinus of the elderly.

Keywords Giant arachnoid granulations · Transverse sinus · Epidemiology

Introduction

Although arachnoid granulations (AGs) were initially described by Antonio Pacchioni more than 300 years ago [1], they are still poorly described, especially in the neuro-radiological literature. Two issues draw particular attention: first, the radiological features of AGs, particularly of the so-called giant AGs (GAGs) and its differential diagnosis [2–11], and second, their possible association with various disease processes [12–14]. Giant AGs are still a poorly understood distinct entity, seldom mentioned in the neuroanatomical and neuropathological literature. Meningothelial hyperplasia is often confused with it. In the latter, putative predisposing factors were recently described and included hemorrhage, chronic renal disease, old age, trauma, and an adjacent optic nerve pilocytic astrocytoma. Furthermore, a discontinuous growth pattern is well known. By definition, meningothelial hyperplasia is a non-invasive process involving the arachnoid mater, which can exist in near proximity to normal tissue or is even surrounded by intact structures [15].

In order to evaluate the frequency, site, size and normal distribution of GAGs, an examination of the dural sinuses was carried out in 651 autopsy cases. In 3.68% of the cases GAGs were found; their morphology and pathophysiological relevance will be discussed.

Materials and methods

In order to evaluate the frequency, size as well as age and sex distribution of GAGs, an anatomical study of the dural sinuses was carried out. It involved all the autopsies performed in the Wagner Jauregg Hospital, Linz, Austria, and its affiliated hospitals in Upper Austria, during the period

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August 2002–February 2005. The study population included 651 cases: 306 females and 345 males, aged 13–99 years (mean 69 years).

The skull was opened in the usual manner and removed carefully, leaving the dura mater intact and covering the brain. Then all intracranial sinuses were opened with scissors and carefully inspected. Any region suspicious for the presence of GAGs, was documented photographically, then excised and processed for histology and subsequent immunohistochemistry. Thus, the specimens were fixed in a 4% formaldehyde solution for 48 h being affixed to a piece of cork. The histological examination encompassed the following stainings: H&E, Elastica van Giesson. Immunohistochemistry was performed on formalin-fixed and paraffin-embedded, 5- μ m-thick sections on adhesive-coated glass. Deparaffinized, rehydrated sections underwent antigen retrieval using 2 mmol/l HCl for 20 min in a water bath at 95–100°C. All subsequent steps were carried out using the DAKO Autostainer Immunostaining System (DAKO S5007) and the EnVision™+ kit (code K4007, DakoCytomation, Carpinteria, CA, USA). The sections were treated with 3% H₂O₂ for 5 min to block endogenous peroxidase followed by protein block for 5 min. The primary antibodies, purchased from DAKO were directed against vimentin, desmin, epithelial membrane antigen (EMA), S100. The sections were incubated with the secondary antibodies for 30 min. The reaction product was visualized using diaminobenzidine chromogen (liquid DAB+, K3468, DakoCytomation, Carpinteria, CA, USA) for 5 min. Then, the sections were counterstained with Mayer's Haemalaun solution. As a second step slides were treated with an enzyme-linked antibody using the system Envision™ DAKO ChemMAT™ Detection Kit followed by peroxidase/chromogene DAB (rabbit/mouse). The following antibodies were used: vimentin (dilution 1:1,000), actin (dilution 1:400), desmin (1:50), S100 protein (dilution 1:800), MiB-1 (dilution 1:200).

The lesions were then classified as AGs or GAGs according to criteria published in the literature as follows: AGs are small protrusions of the arachnoid through the dura. Giant AGs are much larger than normal AGs, approximately 10 mm in diameter.

Immunohistochemistry was evaluated by two independent assessors (J. H. and R. S.) using light microscopy. Furthermore, clinical histories were evaluated with regard to the existence of other diseases/disorders in order to find a correlation with other diseases.

Results

The size of the examined sample encompassed 651 cases: 306 females and 345 males, aged 13–99 years (mean age:

69 years). Grossly visible GAGs were identified in 24 patients: 7 females and 17 males, aged 45–92 years (mean 69 years). No GAGs were observed in individuals younger than 45 years; 20.8% of patients with GAGs were under the age of 65 while 79.2% were 65 years of age and older. The age-specific incidence of our cases was: group 1: <65 years: 36.4%, group 2: \geq 65 years: 63.6% out of entire autopsies with an overall incidence of 2.9%. A histogram showing the age distribution of these lesions in the entire cohort by decade is shown in Table 1; the age distribution of individuals with the definite diagnosis of GAGs in percentage is presented in Table 2.

All GAGs were found exclusively in the transverse sinus, usually adjacent to the transverse/sigmoid sinus junction (Fig. 1). In 13 cases (54.1%) GAGs were found bilaterally, while in the remaining cases they were almost equally divided between the right (5 cases) and the left transverse sinus (6 cases).

Table 1 Histogram showing the age distribution of prevalence of giant AGs in the entire cohort by decade

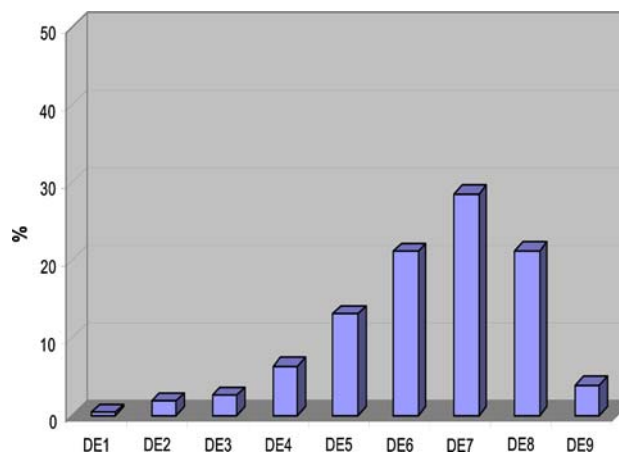


Table 2 Histogram showing the age distribution of prevalence of giant AGs in the positive cases by decade

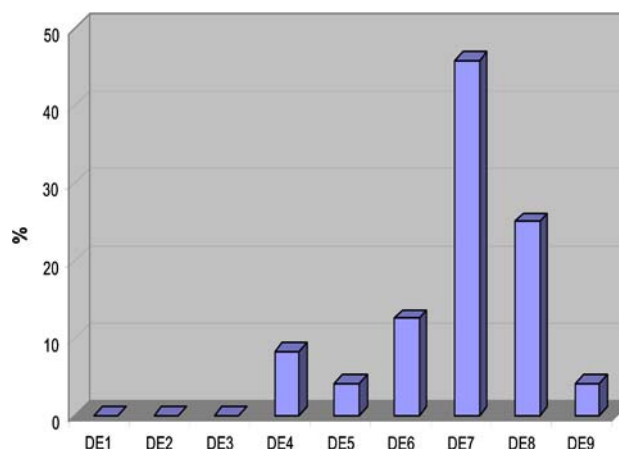
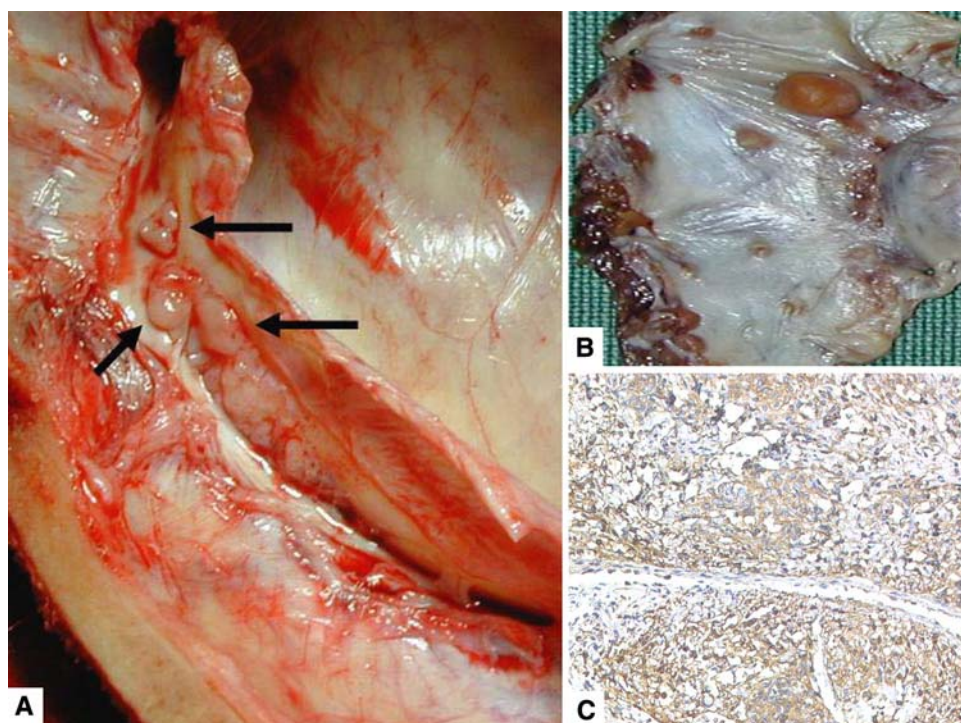


Fig. 1 **a, b** Examples of “giant” AGs (GAGs) in the left transverse sinus underneath the skull of the posterior cranial fosse (macroscopy). **c** GAG stained with an antibody against vimentin ($\times 20$)



Grossly, GAGs appeared as partly gelatinous, partly white-yellowish shiny lobular protrusions into the sinus lumen, usually at sites of cortical venous entrance into the sinus (Fig. 1). Their size ranged from 1 mm to 29 mm in diameter (mean 6 mm), with more than one third of the GAGs (37.6%) being larger than 10 mm in diameter, qualifying as “giant AGs” (size distribution: up to 2.5 mm: 12.5%; 2.6–5 mm: 20.8%; 5.1–7.5 mm: 12.5%; 7.6 mm–10 mm: 16.6%; >10.1 mm: 37.6%). We could neither find a correlation of the size of the GAGs with the age of the patients nor of the presence of malignancies or severe cardiovascular problems and enlarged AGs or any further diseases. Histologically, GAGs were composed of dense collagenous connective tissue admixed with clusters of arachnoid cells and a network of delicate vascular spaces, covered by an endothelial cell layer. Histology showed vascular, cell-free spaces beside broad arachnoidal and dural collagenous bands (Figs. 1, 2).

On microscopic examination of proliferations in the transverse sinus diagnosed on autopsy in 24 patients, a positive reaction for vimentin could be shown in collagenous, hypertrophic lesions. Those tumour-like lesions in the transverse sinuses were negative for actin, desmin and S100 protein on immunohistochemistry (Figs. 1, 2). The proliferative activity was evaluated by the MiB-1 index (KI 67). The fact that GAGs represent a non-neoplastic process was extremely low stressing.

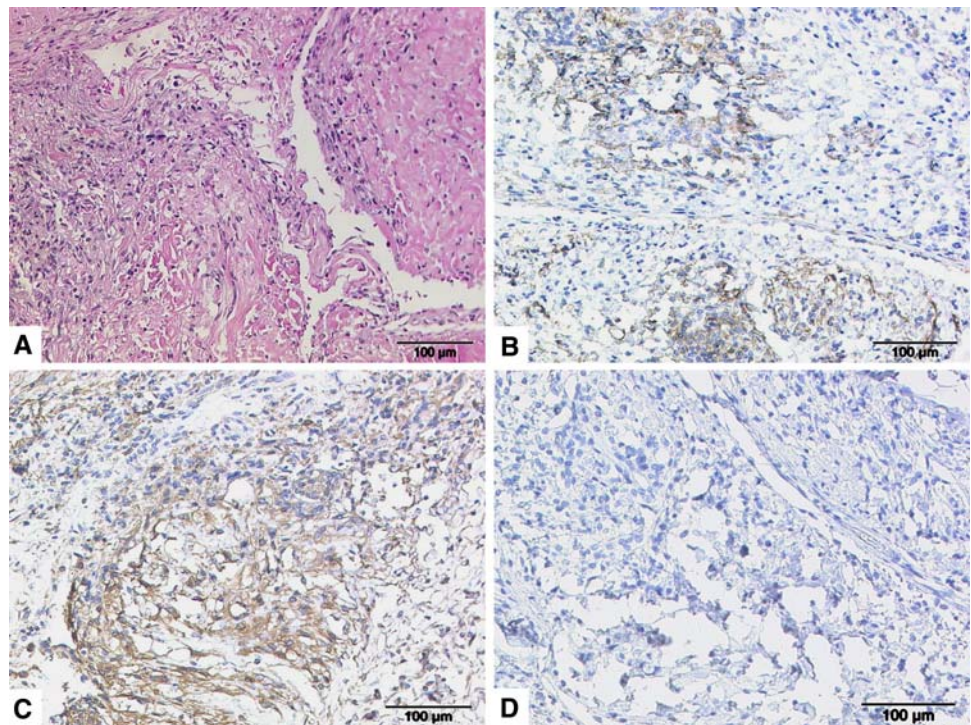
In none of those cases an association with other pathologic findings could be detected.

Discussion

To the best of our knowledge, this is the largest population-based anatomical study on GAGs. It shows that GAGs are rather common in the adult population, especially in the elderly (aged >65 years) and they can reach remarkable proportions (up to 2.5 cm and more in diameter). Giant AGs should be considered in the radiological differential diagnosis of intradural lesions, particularly those occurring in the transverse sinus of the elderly. Interestingly, grossly visible GAGs were exclusively found in individuals older than 45 years, which could be a hint for a degenerative process. Because we could not find in any of the cases a direct association with the patient’s illness or the cause of death this observation represents more a normal anatomic finding rather than a pathologic process. The occurrence of GAGs should be considered in the differential neuroradiological diagnosis of meningiomas, especially benign meningiomas because of their similarity to such lesions [14, 15]. This becomes more crucial, when they are seen in close contact with the skull bone or with the dura mater. As in only 4 of the 24 cases no sclerosis of the cerebral arteries was noted, these proliferate changes must not be considered to represent pathologic changes but rather one may assume that such a hypertrophy develops with higher age.

As a possible differential neuropathological diagnosis, meningotheial hyperplasia has been defined in different ways, for example as meningotheial nests consisting of 3 or 4 cell layers or greater. Based on studies published in the

Fig. 2 **a** H&E stained section of a Giant AG (GAG). Meningothelial cap cells show discrete variations in cytology with not uniform nuclear cytoplasmic ratio. Positively immunoreactive structures for **b** epithelial membrane antigen (EMA) and **c** vimentin in GAGs. **d** No positive immunoreactivity for S100 in GAGs ($\times 20$)



last years on this topic we chose a more conservative cut off of 10 cell layers to diagnose GAGs. Meningothelial hyperplasia is known as a rare abnormality in intracranial sinuses. Clinical symptoms directly caused by these pseudo-tumours are not described in the literature so far. In the present study, we investigated morphological changes in more detail using additional immunohistochemical stains. In autopsy specimens GAGs are often moderately found to be partly gelatinous bright, partly white-yellowish shiny proliferations in the lumen of the intracranial sinuses. Microscopically these tumour-like lesions are positive for vimentin, negative for actin, desmin and S100 protein. On H&E-stained sections, the excrescences impress as meningothelial nested structures.

Although that was not extensively investigated in all sinusal regions, it is most likely that meningothelial hyperplasia may also occur in other intracranial sinuses than only in the transverse sinuses but less frequently. Since the morphological alterations were found only in the transverse sinuses in this study one could interpret this region as “locus minoris resistentiae” considering a degenerative process to be pathogenetic. These granulations develop from the arachnoidea as a soft tissue structure with few vessels into the dura mater and rising up toward venous blood vessels, partly up to the bony skull as so called foveolae granulations and flowing into venes of the diploe. Here they presumably play a role in resorption of cerebrospinal fluid out of the subarachnoid space and for its deposition to the blood stream. It is known from literature that the daily production of this cerebrospinal liquor is about 500 ml a day.

The function of resorption by pacchionian granulations is to prevent higher brain pressure. These regular granulations are often morphologically observed as nests, but with a different morphological pattern.

In other studies, significant observations regarding the immunoprofile of meningiomas have been reported because all previously described stains could not discriminate hyperplastic lesions from totally normal meningeal tissue or benign meningiomas [16, 17]. Up to now the only finely working marker being able to distinguish GAGs from meningothelial hyperplastic lesions is the stain for progesterone receptor. Perry et al. [17] have shown that normal meningeal cells are uniformly negative for PR whereas nuclear positivity is seen in 64% of hyperplasia in their collective forms, similar to that in grade I meningiomas. Giant AGs are also negative for PR. From a genetic point of view many alterations have been described for meningiomas, some for meningothelial hyperplasias but none for GAGs [15].

For differential diagnosis of other meningeal lesions, granulation tissue, scars, inflammatory reactions or vascular proliferations have to be taken into consideration leading to meningiomas as the neoplastic endpoint of the list of possible different functional stages of the meninges. In clinical practice this distinction between reactivity and real neoplastic process has important implications, since a hyperplastic process should be self-limited, whereas a real neoplasia may require a panel of different therapeutic strategies.

According to the theory of physical pressure causing reactive proliferations a correlation between the blood flow

in the intracranial circulation and the occurrence of hypertrophic changes would be extremely interesting, also concerning physiological circumstances in intracranial sinuses and pathological alterations of this region.

Because there are so few studies on GAGs and meningo-thelial hyperplasia, in our opinion, it is time to make these entities more popular. For further studies it will also be exciting to look for such hyperplasias in the vertebral channel, too because it could also occur in this location after trauma, subarachnoidal bleeding, under degenerative circumstances and in developmental injuries such as spina bifida or different types of meningocele or myelocele.

It will be interesting to evaluate more immunohistochemical markers in future studies in order to elucidate the exact origin of the outlining cells standing at the border of the cell free spaces seen on histology. Genetics might finally clarify the open questions.

The take-home message for the neuropathological practice is as follows: the incidence of GAGs lies in the later decades of life (over the 6th decade). A clinical–pathological correlation is not found, although the rate of sclerosis of the cerebral arteries was very high, but probably just because of the sample's high age.

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